

Sex and Gender in Cardiovascular Medicine: Presentation and Outcomes of Acute Coronary Syndrome

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Abstract

Although health-disparities in women presenting with acute coronary syndrome (ACS) have received growing attention in recent years, clinical outcomes from ACS are still worse for women than for men. Women continue to experience higher patient and system delays and receive less aggressive invasive treatment and pharmacotherapies. Gender- and sex-specific variables that contribute to ACS vulnerability remain largely unknown. Notwithstanding the sex differences in baseline coronary anatomy and function, women and men are treated the same based on guidelines that were established from experimental and clinical trial data over-representing the male population. Importantly, younger women have a particularly unfavorable prognosis and a plethora of unanswered questions remains in this younger population. The present review summarizes contemporary evidence for gender and sex differences in vascular biology, clinical presentation, and outcomes of ACS. We further discuss potential mechanisms and non-traditional risk conditions modulating the course of disease in women and men, such as unrecognized psychosocial factors, sex-specific vascular and neural stress responses, and the potential impact of epigenetic modifications.

Introduction

Cardiovascular disease (CVD) remains the most common cause of morbidity and mortality in Europe, accounting for 49% of deaths in women and 40% of deaths in men¹. Over the last four decades, age-adjusted mortality for CVD has continuously declined, however to a lesser extent in women than in men². Most intriguingly, recent studies report a significant increase in case fatality rates of acute coronary syndromes (ACS) in young women <55 years of age, while a decrease in mortality from coronary artery disease (CAD) has occurred in younger men³⁻⁶. Despite growing evidence demonstrating sex and gender differences in baseline risk factors, coronary anatomy and function, symptoms presentation, comorbidities, treatment efficacy, and outcomes of ACS, mechanisms behind these differences are largely unexplored^{6, 7}. These knowledge gaps are nourished by the persistent underrepresentation of women in cardiovascular clinical trials and a lack of basic science evidence obtained from female animals

and cells owing to a manifold refuted concern that inclusion of females will increase variability, and double sample size and costs⁸⁻¹². This review provides a summary of contemporary evidence shedding light on sex and gender differences in the clinical presentation of ACS as well as in diagnostic accuracy of tests, invasive treatment, pharmacotherapy, and outcomes.

Sex Differences in Coronary Biology

Women have significantly smaller epicardial coronary arteries than men, even after adjustment for age, body habitus, and left ventricular mass¹³. Baseline and hyperemic myocardial blood flow, as assessed by positron emission tomography (PET), is typically higher in women as compared to men resulting in a similar global coronary flow reserve (CFR) in men and women^{14, 15}. Although exact mechanisms are lacking, the smaller diameter of female epicardial coronary arteries together with their higher baseline myocardial blood flow have been suggested to result in a significant increase in endothelial shear stress conditions in women¹⁶. Given that low endothelial shear stress has been associated with focal lipid accumulation, pathologic remodeling, and plaque instability¹⁷, it has been hypothesized that higher shear stress conditions in female coronary arteries may contribute to sex differences in susceptibility to CAD¹⁸. These sex differences might be particularly relevant during premenopausal ages owing to estrogen-dependent effects on endothelial mediators such as nitric oxide, prostaglandins, and endothelium-derived hyperpolarizing factor^{19, 20} (Figure 1). The vascular actions of estrogen are primarily mediated via estrogen receptor α signaling promoting an anti-inflammatory, low-vascular-resistance phenotype that is protected from CVD²¹. Estrogen receptor α -mediated effects are blunted in the absence of estrogen which is consistent with variations seen in vascular stiffness throughout the lifespan of women²². Importantly, increased vascular stiffness strongly correlates with blood pressure, diastolic dysfunction, impaired ventricular coupling, and left ventricular remodeling and is thought to play a role in disease conditions preferentially affecting postmenopausal women such as heart failure with preserved ejection fraction (HFpEF) or isolated systolic hypertension²³. Finally, women display distinct coronary plaque characteristics with a more diffuse and non-obstructive disease pattern,

reduced overall plaque burden, and calcium content as well as less signs of necrosis in the plaque core²⁴ (Figure 1). Accordingly, while plaque rupture is the primary mechanisms responsible for myocardial infarction in men, plaque erosion is the major cause of coronary thrombosis in women, particularly in premenopausal women^{25, 26} (Figure 2). Despite an overall lower plaque burden in women, coronary artery calcium scoring has recently been demonstrated to be a stronger risk predictor for future cardiovascular events in women as compared to men²⁷. Thus, coronary artery calcium scoring has been recommended for evaluation of asymptomatic women with a 10-year CVD risk >7.5% by a recent expert consensus statement²⁸.

Influence of Sex and Gender on Cardiovascular Risk

Traditional Risk Factors

Although traditional risk factors for CVD are the same in women and men, differences in prevalence and impact of these risk factors vary between men and women^{29, 30} (Figure 3). This is especially seen in ACS, as women who present with ACS are generally older and have more comorbidities, including a higher prevalence of hypertension, dyslipidemia, diabetes, heart failure, and atrial fibrillation^{31, 32}. Women with early-onset type 1 and type 2 myocardial infarction (MI)³³ have received growing attention as a group affected by inequalities in health outcomes^{4, 34}. Mechanisms for these differential outcomes are unclear, but data from the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study indicate that younger women have a worse pre-event health status versus men, including lower overall and mental health qualities of life³⁵. Smoking, like diabetes mellitus, has been shown to have a stronger impact on women, as there is a 25% increased risk for fatal and non-fatal cardiovascular events in female smokers as compared to male ones, independent of other risk factors³⁶⁻³⁸ (Figure 3). Smoking-related cardiovascular risk was highest among young and middle-aged women³⁶. Diabetes also carries a differential risk between sexes, with diabetic women being at significantly higher risk of developing CAD or HFpEF than their male counterparts³⁹⁻⁴² (Figure 3). Finally, a significant role in the case of younger women is also

played by family history as women <65 years with a maternal history of MI encounter a four times higher risk of ACS than same aged men or older women⁴³.

Non-traditional Risk Conditions

Data emerging from the VIRGO study indicate that young and middle-aged women hospitalized for type 1 and type 2 MI were more likely to have lower socioeconomic status, higher levels of psychosocial burden, such as depression and poorer physical/mental health, and overall lower quality of life compared to men⁴⁴ (Figure 2). Accordingly, depression, trauma, and perceived stress have been identified as powerful predictors of cardiovascular risk in young and middle-aged women^{45, 46}. This trend is not surprising, given that psychosocial stress has substantially increased for women during the last two decades due to a continuous increase in women's economic participation and educational attainment⁴⁷. Further, low socioeconomic status is an established variable inversely associated with global coronary risk and imposes a higher excess risk on women as compared to men⁴⁸ (Figure 2). Of note, recent work states that feminine roles and personality traits, but not female gender itself, are associated with higher rates of ACS as compared to masculine characteristics, however, objective evidence of this vulnerability is still insufficient⁴⁹.

It is increasingly appreciated that the gut microbiome, harboring trillions of microbial cells, plays an important role in the development of CAD⁵⁰⁻⁵². Indeed, systemic trimethylamine N-oxide levels – a pro-atherogenic and pro-thrombotic metabolite produced by the gut microbiome – was shown to predict 30-day and 6-month event-free survival in women and men with suspected ACS^{53, 54}. In addition, there is emerging evidence for sex differences in microbiome-mediated contribution to cardiovascular risk factors and comorbidities including inflammatory processes, autoimmune disease, cardiometabolic disorders, and major depression⁵⁵⁻⁵⁷. Men and women have different genetic backgrounds, energy and nutritional requirements across the lifespan, as well as differences in gastrointestinal transit time, which can contribute to sex differences in microbiome⁵⁸. Future studies will show the potential of gut

microbes to provide novel diagnostic and therapeutic targets tailored to the female and male cardiovascular system.

Female-specific Risk Factors

Premenopausal women are thought to be relatively protected against CVD as compared with age-matched men, with early menopausal transition and postmenopausal status shown to be associated with adverse risk for CVD and mortality^{59, 60}. Estrogen withdrawal at menopause has many negative effects on cardiovascular function and metabolism, including alterations in body fat distribution, endothelial dysfunction, vascular inflammation, sympathetic tone, and a higher insulin resistance contributing to hypertension,^{61, 62}. In fact, menopause is accompanied by an accelerated age-related rise in cardiac and peripheral sympathetic nerve activity, most likely related to an impaired central modulation of baroreflex function or a direct inhibitory influence of estrogen on sympathetic nerve activity^{63, 64}. However, although initially supported by large observational studies^{65, 66}, randomized controlled trials largely failed to show any cardiovascular benefit of menopausal hormone replacement therapy (HRT) and even demonstrated an increased event rate in postmenopausal women with a recent ACS⁶⁷⁻⁶⁹. Thus, the use of HRT for primary and secondary prevention of CVD remains controversial and is currently not recommended^{70, 71}. However, a re-analysis of the Women's Health Initiative data led to the so called 'timing hypothesis', indicating that HRT might be beneficial when initiated during early menopause⁷²⁻⁷⁴. Notably, while these data suggest that specific subgroups of postmenopausal women might profit from HRT, the use of estrogen-containing contraceptives in premenopausal women with known CVD is generally not recommended⁷⁵. In fact, although the risk is small in absolute numbers, combined oral contraceptives have been associated with hypertension as well as a significant increase in venous and arterial thrombosis⁷⁶⁻⁷⁸.

Interestingly, changes in iron status have been suggested as an alternative mechanism accounting for the risk increase seen in postmenopausal women. Indeed, concurrent but inverse alterations occur between iron and estrogen levels in healthy women during menopausal transition; whereas estrogen decreases because of the cessation of

ovarian functions, iron increases as a result of decreasing menstrual period⁷⁹. Higher iron plasma levels and associated alterations in iron metabolism after early-onset menopause are believed to exert detrimental effects on the cardiovascular system via induction of inflammatory cascades⁸⁰. Conversely, several observational reports claim that iron deficiency independently predicts adverse cardiovascular outcome in women and men⁸¹⁻⁸³. Thus, the iron hypothesis remains controversial owing to the lack of adequately designed clinical trials and the fact that current biomarkers of iron status are not validated. As iron deposits in the heart tissue might impact cardiovascular endpoints, T2 star (T2*) cardiac magnetic resonance imaging may offer an opportunity to improve our mechanistic understanding for the role of iron in CAD⁸⁴.

Pregnancy is often quoted as providing a glimpse into a woman's future health status with numerous pregnancy-related complications associated with increased cardiovascular risk⁸⁵. A recent meta-analysis concluded that the risk of CAD was highest in women with a history of preeclampsia, placental abruption, gestational hypertension, and diabetes⁸⁶ (Figure 2). Moreover, the development of gestational diabetes has been shown to increase the risk for CAD by two to three-fold even 25 years after delivery⁸⁷, while preterm delivery (<37 weeks gestation) in the first pregnancy was independently associated with a 1.5-fold increased risk of CAD⁸⁸. Notably, a combination of these risk factors seems to potentiate cardiovascular risk as the occurrence of major coronary events and mortality was nearly six-fold increased after preeclampsia in combination with preterm delivery and/or infants born small for gestational age⁸⁹. Accordingly, adding pregnancy complications to traditional risk models led to significant improvements of CVD risk prediction among a representative sample of Norwegian women⁹⁰.

Potential Future Risk Marker: Epigenetic Modifications

Epigenetic modifications of the genome might constitute a novel pathway leading to sexual dimorphism in ACS. DNA-methylation (DNAm), the best-understood epigenetic modification, defines cell's identity, and it is vital for normal cellular processes and adapting cells to environmental changes⁹¹. However, dysregulated DNAm contributes to adverse changes in gene expression and may affect cardiovascular risk factors including obesity, atherosclerosis,

inflammation, hypertension, blood lipids, and glucose metabolism, subsequently leading to increased risk of developing CAD⁹²⁻⁹⁴. Although epigenetic mechanisms have emerged as potential future risk factors in CVD, this field of research is still in a pioneer stage; to date, few studies with small sample sizes have investigated associations of DNAm with ACS. Of note, Li D et al. reported that more than 11,000 differentially methylated CpGs exist between ACS cases and controls, thereby covering 5,071 genes involved in ACS-related biological processes⁹⁵. Similarly, differences in DNAm of ANGPTL2, a pro-inflammatory gene, were found in post-ACS patients as compared to their healthy age-matched controls⁹⁶. Sex differences at the level of DNAm and associations of global and gene-specific DNAm with traditional risk factors have been described, supporting the hypothesis that epigenetic mechanisms may play a role in shaping sex differences in ACS⁹⁷⁻¹⁰⁷ (Figure 4). However, despite epigenetics being increasingly linked to sexual dimorphism in the cardiovascular system, there is lack of adequately designed epigenetic studies assessing sex-specific effects of epigenetics in the development of ACS.

Mental Stress and Myocardial Injury

Recent data indicate that women, especially young women, are particularly vulnerable to the detrimental associations of mental stress and cardiovascular health¹⁰⁸⁻¹¹¹ (Figure 2). Accordingly, women seem to perceive greater psychological stress following an acute type 1 or type 2 MI as compared to men, which, in turn, is associated with worse recovery and prognosis¹¹². As young women with ischemic heart disease are a group with unexplained high mortality, these gender differences in mental stress responses are of particular importance and emphasize the need for a better evaluation of the psychosocial domain in order to risk stratify these women. The underlying psychological and biological mechanisms accounting for the adverse vascular response to psychological stress in women are not well understood. Besides vascular determinants, variation in baseline sympathetic activity and women's propensity towards microcirculatory abnormalities¹¹⁰, excess serotonin, a worse overall mental health status in women³⁵, as well as a differential activation of the limbic system and the

hypothalamic–adrenocortical axis in men and women are notable. Indeed, women have higher baseline cardiac sympathetic activity and excessive sympathetic discharge after an acute type 1 MI than men^{64, 113}. Further, a link between the limbic system and long-term cardiovascular outcomes has recently been demonstrated¹¹⁴ and gender-stratified data indicate that this link might be pathogenic in women, but not in men¹¹⁵.

Ischemia and Non-obstructive CAD (INOCA)

Increasing evidence supports the notion that obstructive CAD alone is insufficient to explain symptoms of myocardial ischemia¹¹⁶. Indeed, microvascular angina, defined as symptoms and objective evidence of myocardial ischemia along with non-obstructive CAD (<50 % coronary diameter reduction and/or fractional flow reserve >0.80) and a reduction of CFR and/or inducible microvascular spasm¹¹⁷, affects approximately 50% of patients with non-obstructive CAD or normal imaging findings¹¹⁸. Despite the absence of obstructive epicardial stenosis in these patients, they may present with severe myocardial ischemia (ischemia and non-obstructive CAD, INOCA) or even MI (myocardial infarction and non-obstructive CAD, MINOCA). These conditions are more frequently observed in women, given the lower burden of obstructive CAD in the female population (Figure 2). In fact, the presence of microvascular angina is twice as prevalent in women than men¹¹⁸. The former portends a particularly high risk in women, as event-free survival is reduced in women with impaired CFR or coronary reactivity^{119, 120}. As PET-derived CFR reflects the hemodynamic effects of focal, diffuse and microvascular CAD on myocardial tissue perfusion, impaired CFR seems to be an important target for CMVD risk reduction in women. Indeed, CMVD might also contribute to the pathogenesis of heart failure with preserved ejection fraction, another condition more commonly observed in women¹²¹. Thus, is it crucial that symptomatic patients who do not show regional ischemia associated with flow-limiting epicardial CAD undergo further testing. Although some studies demonstrate an improvement of prognosis by revascularization therapies (coronary artery bypass grafting, CABG) in patients with severely impaired CFR¹²², treatment of coronary microvascular disease (CMVD) usually includes standard anti-ischemic

drugs (β -blockers, angiotensin converting enzyme inhibitors, and nitrates). The diagnosis of CMVD requires a complex diagnostic work-up such as myocardial perfusion PET or invasive vasoreactivity testing; thus, optimal clinical assessment and pre-test risk stratification is crucial in order to avoid unnecessary costs and risk. In this regard, a blunted heart rate response during pharmacological stress testing has recently been shown to be a strong predictor of impaired CFR in women and may be a helpful marker to risk stratifies the heterogeneous population of patients with non-obstructive CAD¹⁵.

Gender and Symptoms of Myocardial Ischemia

Chest pain or pressure is the presenting symptom in >80% of women and men with ACS. However, women present with a greater number of additional non-chest pain symptoms than men such as neck pain, fatigue, dyspnea or nausea¹²³. Further, women are more likely than men to present without chest pain and more often attribute their symptoms to a non-heart-related condition such as acid reflux, stress or anxiety¹²³. Also, women in general wait longer to seek medical attention and are less likely to have diagnostic electrocardiography changes and elevated troponin levels on admission¹²⁴⁻¹²⁶ (Figure 3). Accordingly, women are at an increased risk for an incorrect diagnosis and delayed treatment as evidenced by numerous studies reporting substantial system delays in women¹²⁵⁻¹²⁷. In addition, women who present with ACS tend to be older and have more comorbidities than their male counterparts¹²⁸. Of note, however, young age and the absence of chest discomfort are among the strongest predictors of a missed diagnosis of ACS and inappropriate discharge from the emergency department¹²⁹. Further, recent observational studies in younger demographic groups report a higher prevalence of comorbidities including depression, hypertension, diabetes, and obesity in younger women with ACS as compared to age-matched men, suggesting that gender-disparities in effective management and outcomes of ACS cannot be attributed to age alone¹³⁰.

Differential Diagnosis of ACS

Contemporary strategies for managing patients presenting with typical or atypical symptoms, an abnormal electrocardiography and raised serum troponin presume a diagnosis of an acute type 1 MI. However, in up to 10% of all patients, and in up to one third of female patients, no culprit coronary lesion is identified angiographically^{131, 132}. In these cases, the differential diagnosis includes apparently non-significant CAD such as plaque erosion, arrhythmias, coronary vasospasm (CVS), spontaneous coronary artery dissection (SCAD), Takotsubo cardiomyopathy, and myocarditis (Figure 3). While magnetic resonance imaging studies indicate that the latter seems to be present in the majority of cases where a culprit lesion is not identified¹³³, a high index of suspicion for Takotsubo cardiomyopathy, CVS, and SCAD should be maintained when evaluating women^{134, 135}. Takotsubo cardiomyopathy is characterized by transient left ventricular dysfunction resulting from severe emotional stress and usually resolves with a favorable prognosis. Although Takotsubo cardiomyopathy only accounts for up to 3% of all ACS cases, it is twice as prevalent in postmenopausal women¹³⁴ (Figure 3).

SCAD is an infrequent and often missed differential diagnosis of ACS and is characterized by a spontaneous separation of coronary arterial layers ultimately leading to intramural hematoma and impairment of anterograde coronary blood flow¹³⁶. Recent epidemiological series suggest that SCAD occurs in 1–4% of ACS cases and may be the cause of ACS in up to 35% of women ≤50 years of age and in 43% of pregnancy-related ACS¹³⁶ (Figure 3). The latter is associated with a poorer prognosis than pregnancy-unrelated SCAD¹³⁷. In-hospital mortality rates of SCAD are low, however, up to 14% of patients require urgent in-hospital revascularization. Non-atherosclerotic SCAD is typically associated with female sex, multiparity, physical, and emotional stress triggers, systemic arteriopathies including fibromuscular dysplasia, inflammatory, and connective tissue disorders, coronary artery spasm, and hormonal therapy¹³⁶. Although hormonal changes seem to play a major role in female SCAD, much remains to be explored on detailed molecular mechanisms by which sex hormones modulate arterial wall architecture and endothelial function.

CVS is caused by intense vasoconstriction of coronary arteries occurring most often at rest, particularly between midnight and early morning. Although the prognosis is generally considered benign, CVS can lead to total or subtotal vessel occlusion and subsequent ACS. CVS is diagnosed by coronary angiography and provocative testing and has been detected in 49% of patients with ACS in a German population¹³⁸. CVS appear to be more prevalent among men than women affecting mainly age groups between 40 and 70 years, and is more common in Asian populations as compared to Western countries¹³⁹ (Figure 2). Vascular mechanisms triggering CVS episodes include transient sympatho-vagal imbalance as well as decreased bioavailability of vasodilators such as nitric oxide^{140, 141}. Age, high-sensitivity C-reactive protein, and smoking have all been identified as significant risk predictors of CVS¹³⁹. The latter has been suggested to account for the higher prevalence of CVS seen in men.

Diagnosis and Disease Management of ACS

Another issue remaining actively debated is whether there are still inequities in diagnosis and disease management, leading to gender-disparities in outcomes among patients with ACS. An excess risk for mortality in women with ACS, in particular for younger women, persists in contemporary practice¹⁴². Female coronary pathophysiology such as a higher prevalence of CMVD and non-obstructive CAD, atypical symptoms, delay in seeking care, underutilization of evidence-based diagnostics and therapies, and a higher rate of complications during revascularization have all been suggested to account for these findings. Indeed, management strategies for ACS have largely been the same for women and men while focused predominantly on obstructive CAD: risk stratification schemes for ACS including the HEART, the Global Registry of Acute Coronary Events (GRACE), and the Thrombolysis in Myocardial Infarction (TIMI) risk scores as well as the Killip classification are derived from predominantly male populations and their ability to adequately risk-stratify women with suspected ACS remains debatable¹⁴³. Similarly, current clinical practice does not consider sex-specific cut-off values for cardiac troponin given the small differences in high sensitive troponin I between men and women. However, evidence demonstrates improved risk stratification in patients with ACS

when a sex-specific 99th centile threshold of high sensitive troponin I is being used¹⁴⁴. Whether the lack of sex-specific guidelines or the high percentage of women presenting with atypical symptoms and comorbidities account for the fact that women are less likely than men to undergo invasive revascularization remains to be determined^{145, 146}. In addition, low adherence to prescribed therapies as well as underutilization of cardiac rehabilitation and pharmacotherapies in women with ACS has also been reported¹⁴⁷. Indeed, women are less likely than men to receive optimal secondary prevention with anti-platelet and lipid-lowering therapies even after angiographic documentation of disease^{146, 148, 149}. These disparities persist in contemporary practice, despite studies documenting the reduction of this excess mortality when optimal care is provided¹⁵⁰.

Outcomes of ACS in Women and Men

Short- and Long-term Mortality

Although there is evidence that gender-disparities in short-term ACS mortality can be overcome in high-quality percutaneous coronary intervention (PCI) centers¹⁵¹, studies have consistently demonstrated less favorable short-term outcomes in women with ACS as compared to men, particularly after ST-elevation myocardial infarction (STEMI)^{1, 152, 153}. The female susceptibility to adverse short-term outcomes following STEMI was attributed to their older age at presentation, the higher prevalence of comorbid conditions in women as well as longer system delays and underutilization of guideline-directed therapies in women with ACS^{150, 154, 155}. Accordingly, sex and gender differences were attenuated when adjustment for comorbidities was performed¹⁵⁶. In contrast to short-term outcomes, gender-specific data regarding long-term morbidity and mortality following ACS are conflicting. While long-term outcomes were similar for women and men in earlier studies, more recent work indicates that long-term morbidity and mortality following ACS is higher in women as compared to men, though these gender-disparities are no longer evident following adjustment for baseline variables¹⁵⁷⁻¹⁵⁹. Of note, however, studies report consistently worse short- and long-term outcomes in young and middle-aged women as compared to age-matched men¹⁶⁰⁻¹⁶³. As

previously discussed, this demographic group presents with an overall worse health status and encounters significant system delays and inequities in diagnosis and treatment, all of which might explain the excess risk in this population ^{4, 5, 164}.

Outcomes of Coronary Revascularization

Current guidelines recommend immediate coronary angiography in patients with type 1 MI - STEMI as well as in patients with type 1 MI - NSTEMI (Non ST-elevation myocardial infarction) presenting with refractory angina or electrical/hemodynamic instability independent of gender. An early invasive strategy (within 24 hours of diagnosis) is recommended for individuals with NSTEMI and stable clinical presentation but high-risk features according to current (gender-unspecific) risk scores^{165, 166}. Benefits of an early invasive strategy have been proven for both, men and women, while a very early invasive strategy within 12 hours of diagnosis improved outcomes in high-risk NSTEMI patients, but did not benefit women^{167, 168}. Of note, despite an overall benefit of invasive revascularization, female sex has consistently been associated with an increased risk of bleeding and vascular complication during PCI^{169, 170} which underscores the need to consider key biological differences such as vessel size and prevalence of non-obstructive CAD and to strictly apply guideline-directed care in women. Indeed, an increased risk of restenosis, repeat revascularization, and access-site complications in women attributable to their smaller coronary arteries and the frequent occurrence of radial artery vasospasm and subsequent radial-to-femoral access crossover all need to be taken into account when treatment decisions in women are made^{171, 172} (Figure 2 and 3).

While there are currently no gender-specific data available on outcomes in patients with AMI unsuitable for PCI who undergo early CABG, observational studies report higher risks for short- and long-term mortality following CABG in women as compared to age-matched men, even when adjusted for age and comorbidities¹⁷³⁻¹⁷⁶. Instead, perioperative complications seem to be similar in women and men, except for a higher incidence of sternal wound infections in female patients¹⁷⁷. Women's smaller arteries and the challenges of surgical grafting to smaller targets, a longer cross-clamp time per graft, a lesser use of internal mammary artery

grafts in women, and a worse preoperative health status in women might all account for the gender differences in outcomes following CABG surgery.

Importantly, recent studies report a significant increase in the incidence of ACS in pregnant women³. The latter is consistent with the recent rise seen in prevalence of CAD in younger, premenopausal women^{4, 5}. According to latest European Society of Cardiology guidelines, primary PCI is recommended in pregnant patients with acute type I MI – STEMI consistent with standard indications for revascularization (class I recommendation), while a non-invasive approach is favored in stable, low-risk patients with type 1 MI - NSTEMI (class IIa recommendation)¹⁷⁸.

Risk of Thrombosis and Bleeding

The risks of thrombosis and bleeding differ between men and women. These sex differences have been attributed to the higher age of women with ACS, comorbidities, and body weight¹⁷⁹. In addition, women experience fluctuations of pro-thrombotic activity and hemostasis that are related to the menstrual cycle, the use of hormonal contraceptives or HRT, pregnancy, and menopause^{179, 180}, all of which might contribute to sex differences in the thrombotic or hemorrhagic burden in women with ACS. Indeed, the higher risk of bleeding complications during PCI observed in women might in part be related to an estrogen-dependent increase of prostacyclin secretion and nitric oxide bioavailability as well as a direct inhibitory effect of estrogen on platelet aggregation¹⁸¹⁻¹⁸⁴. Of note, however, there is conflicting evidence regarding sex differences in baseline and on-treatment platelet reactivity¹⁸⁵⁻¹⁸⁸. In fact, while some studies report a more pronounced platelet adhesion to the site of injury in men as compared to women¹⁸⁹, others have demonstrated a greater baseline and agonist-induced platelet reactivity and aggregation in women^{181, 185, 190-192} (Figure 1). The latter contrasts with an up to 25% longer *in vivo* bleeding time in women as compared to men. Thus, further research is necessary to disentangle the complex interaction between hemostasis, sex, and hormone status at baseline and in the context of an ACS. In mainly postmenopausal cohorts, smaller arteries and related access-site complications as well as inappropriate dosing of anti-

thrombotic agents irrespective of body weight have been suggested to account for their excess bleeding risk¹⁹³. Indeed, female sex was associated with an enhanced risk of non-bypass-related bleeding events in the prasugrel and ticagrelor arms of the TRITON-TIMI 38 and the PLATO trials^{194, 195}. In contrast, no interaction between female sex and excess bleeding was seen in a meta-analysis comparing clopidogrel plus aspirin vs aspirin¹⁹⁶, and a recent meta-analysis reported a comparable efficacy and safety profile of potent P2Y₁₂ inhibitors including prasugrel, ticagrelor, and intravenous cangrelor in women and men¹⁹⁷. In contrast, however, recent data from the CRUSADE initiative indicate that women with type 1 MI - NSTEMI were more likely to receive excess glycoprotein (GP)IIb/IIIa doses than men, with the latter being associated with an increased risk of bleeding¹⁸³. Taken together, these data indicate that sex should not influence patient selection for the administration of P2Y₁₂ inhibitors; however, special attention has to be paid in women to properly apply weight- and age-adjustments of anti-thrombotic agents including GPIIb/IIIa inhibitors, heparins, and prasugrel. Indeed, up to one fourth of sex-related differences in bleeding risk seem to be avoidable¹⁸³.

As outlined above, a significant rise in the incidence of ACS is currently being observed in pregnant women³. Pregnancy is a pro-coagulant state, aimed at preventing bleeding at the time of delivery and is characterized by an increase in the levels of coagulation factors, fibrinogen, and von Willebrand factor, a reduction of activity of protein S and C, and an increase in plasminogen activator inhibitor type 1 and 2¹⁸⁰. Unfortunately, current guidelines provide little information regarding the use of anti-platelet therapy in pregnant women with ACS. A recommendation is only given for aspirin, short-term heparinization during PCI and for clopidogrel, which should solely be used when strictly necessary and for the shortest duration. The use of GPIIb/IIIa inhibitors, bivalirudin, prasugrel, and ticagrelor is not recommended due to the lack of data in pregnant women¹⁷⁸.

Conclusion and Outlook

Although substantial progress has been made towards improving gender- and sex-specific ACS disease management and outcomes, contemporary reports indicate a persistent knowledge gap with regard to optimal risk-stratification and management in female ACS patients. Prominent patient and system delays in women with AMI result from limited awareness for the latent CVD risk in women, a lack of sex-specific thresholds within clinical guidelines, and subsequent limited performance of contemporary diagnostic approaches in women, all of which are the result of a persistent underrepresentation of women in cardiovascular studies¹⁰. In addition, little is known about the influence of socio-environmental and contextual factors on gender-specific disease manifestation and outcomes. Thus, future research will have to overcome barriers accounting for the low numbers of women enrolled in ACS trials and to explore sex and gender differences in biology, environment, and psychosocial complexity. Finally, improved interdisciplinary and cooperative care in women's health has recently been suggested as an attractive model to target cardiovascular health inequalities between women and men linked to modifiable risk factors and social determinants of health⁹⁵.

Figure Legend

Figure 1: Effects of estrogen and testosterone on plaque development, atherothrombosis, coagulation, and vascular injury and healing. Evidence from experimental and clinical studies. LDL, low density lipoprotein; VSMC, vascular smooth muscle cell; EC, endothelial cell; CRP, c-reactive protein; TNF- α , tumor necrosis factor- α ; IFN γ , interferon γ ; IL, interleukin; CCL2, C-C Motif chemokine ligand 2; F, factor; PAI-1, plasminogen activator inhibitor-1; eNOS, endothelial nitric oxide synthase; EDHF, endothelium-derived hyperpolarizing factor; PGI₂, prostaglandin I₂; ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate; VEGF, vascular endothelial growth factor; WBC, white blood cell; VCAM-1, vascular cell adhesion protein 1; TXA₂, thromboxane A₂; ADP, adenosine diphosphate; Bcl-2, B-cell lymphoma 2 (inhibitor of apoptosis); STAT3, signal transducer and activator of

transcription 3; ATP, adenosine triphosphate. *Controversial data exist with regard to the effect of estrogen and testosterone on platelet aggregation responses and myocardial injury.

Figure 2: Mechanisms and characteristics of myocardial ischemia in women and men. FFR, fractional flow reserve; INOCA, Ischemia and No Obstructive Coronary Artery Disease; MINOCA, Myocardial Infarction with No Obstructive Coronary Artery Disease.

Figure 3: Sex differences in pathophysiology, presentation and outcomes of acute coronary syndromes (ACS). ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection.

Figure 4: Sexually dimorphic epigenetic regulation of acute coronary syndrome (ACS). Potential sex-specific interplay between environmental changes, cardiovascular risk factors and epigenetic modifications (e.g. DNA methylation or histone modification) impacting atherosclerotic plaque development and cardiovascular risk during a lifetime. ACS, acute coronary syndrome; cRNA, coding RNA; DNA, deoxyribonucleic acid; miRNA, micro RNA; lncRNA, long non-coding RNA; RNA, ribonucleic acid.

500 **References**

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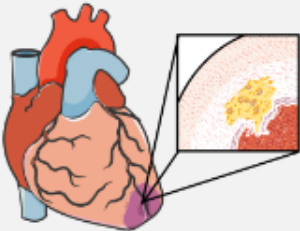
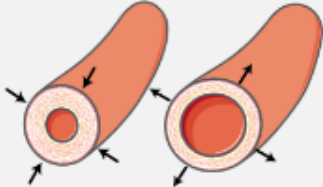

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	Estrogens	Testosterone
Atherosclerosis Risk Factors 	LDL oxidation↓ LDL binding↓ VSMC proliferation↓ VSMC migration↓ EC proliferation↑ EC migration↑ CRP↑ Pro-inflammatory (TNF- α , IFN γ , IL-6, CCL2) cytokine production↑ Hematopoietic stem cell differentiation↑ Coronary calcification↓	Conflicting effects on lipids Expression of pro-atherogenic genes↑ WBC adherence to EC↑ Pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6, IFN- γ)↓ CRP↓ IL-10↑ Plaque volume↑, VCAM-1 expression↑ (controversial data) Coronary calcification↑
Thrombus Formation 	Coagulation factors (FVII, X, XII, XIII), pro-thrombin fragments↑ PAI-1↓ Collagen-induced platelet activation/aggregation↓↑* Baseline platelet activity↑ Release of mast cell proteases and TNF- α ↓	Platelet inhibition by PGI ₂ ↑ Platelet response to ADP↑ TXA ₂ platelet aggregation↑ Plasma fibrinogen level↑ Infarct size↓, protection from ischemic injury*
Vasoreactivity 	Vasodilatation eNOS activity↑ Nitric oxide bioavailability↑ EDHF-mediated relaxation↑ Endothelin↓ PGI ₂ ↑ Sympathoadrenal responsiveness↓ Blood pressure↓	Vasodilatation (coronaries) via inhibition of L-type Ca ²⁺ channels Vasoconstriction (aorta) Attenuation of the vasodilatory effect of adenosine Endothelium-independent VSMC relaxation↑ Thromboxane A ₂ synthase↑ Blood pressure↑
Vascular Apoptosis 	Mitochondrial ROS production↓ Antioxidant defense mechanism↑ Antioxidant gene expression↑ NADPH oxidase activity↓ Endothelial progenitor cells↑ EC apoptosis↓ VEGF expression↑ EC proliferation↑ EC migration↑	Pro-apoptotic effect (Caspase-3↑ Bcl-2↓) Apoptosis following ischemia/reperfusion injury↓ via STAT3 activation↑ Mitochondrial stabilization via K _{ATP} channels following ischemia/reperfusion injury↑

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